SUPPLEMENTAL POLICIES

DRUG USE IN AQUACULTURE ENFORCEMENT PRIORITIES

I. Purpose:

This guide describes enforcement priorities which apply to drugs for use in aquaculture food species/populations.

II. Priorities for Regulation of Drug Use in Food Species/Populations:

A. Enforcement Priorities by Segment of Industry.

1. Drug Manufacturers:

Primary focus among drug manufacturers and distributors will be on firms that specialize in manufacturing for, and distributing to, the aquaculture industry. Special attention should be given to distribution of high priority drugs; possible diversion and abuse situations, e.g., promotion for food species use of drugs labeled for nonfood species; and packaging of "nonfood fish" drugs in commercial pond-size containers.

If intended drug use of a multi-purpose chemical is not established by labeling, or by overt acts by the vendor (e.g., promotion), enforcement actions against the vendor would have to be based on case-by-case analysis. See 21 CFR 201.128.

2. Feed Manufacturers:

Priorities will be determined on a case-by-case basis. For firms required to be licensed to manufacture medicated feeds and veterinary feed directive drugs, inspections and enforcement actions will be handled according to relevant compliance guidelines.

3. Producers:

Primary emphasis with producers will be on education with emphasis on proper drug usage, e.g., which drugs are permitted and how to comply with Hazard Analysis Critical Control Points (HACCP). There will be no routine inspections for enforcement purposes. This will not preclude surveys to determine usage patterns for drugs, sources of the drugs, etc.

"For cause" inspection assignments will encompass either individual producers, or could be more broadly based. Such inspections might include, for example, (a) follow-up where a residue was found at a processing plant and (b) a situation in which there is reason to believe that producers might be holding significant quantities of a drug of high enforcement priority (such as malachite green) and regulation at the manufacturer/distributor level is not feasible.

4. Processors:

Although inspection and sampling at processing plants is ordinarily beyond CVM's jurisdiction, CVM has two major roles: (a) assisting in establishing priorities for methods development for animal drug residues, and (b) working with the Office of Seafood, CFSAN, and the Field to provide for follow-up where illegal drug residues are found. It should also be noted that many of the larger aquaculture facilities are affiliated with processing plants.

B. Determination of Enforcement Priorities for Particular Drugs

The primary long range goals in enforcement prioritization will be to protect public health and encourage submission of INADs and NADAs with a view toward obtaining approvals to meet therapeutic and production needs in aquaculture.

1. In general, drugs for use in food species will be categorized as follows:

a. High priority for enforcement action;

b. Other drugs for which INADs/NADAs will be required, i.e., the drugs cannot be marketed or used unless they are “subject of investigational or new animal drug applications;” and

c. Low priority for enforcement action (INADs/NADAs will not be

required).

2. Drugs will be categorized at CVM's initiative or on request of an interested party. In the latter case, the requestor will be asked to provide available data and information that the Center can use to determine enforcement priority.

3. In general, regulatory action will be taken in each case where a high priority drug (II.B.l.a. above) is found. In addition, such drugs may be subject of special assignments to the Field. Drugs in category II.B.l.b. (other drugs for which INADs/NADAs will be required) will be subject to regulatory action on a case-by-case basis, based on the factors listed below.

4. Factors to consider in establishing enforcement priority:

   a. Jurisdiction -- Is the article a drug? Is it within the jurisdiction of another center (e.g., CFSAN) or agency (e.g., EPA)?

   b. Approval status of the active ingredient:

      (1) If FDA has withdrawn the approval of the active ingredient for human food safety reasons, the enforcement action will be given a high priority;

      (2) If FDA has withdrawn the approval of the active ingredient for other reasons, priority will be determined on a case-by-case basis; and

      (3) If an approved animal drug product containing the same active ingredient is available, the drug will ordinarily not be low priority.

   c. Approval status of drugs with different active ingredients but similar uses.

   d. Scientific/medical criteria (based on a review of the chemical(s) and formulation, and conditions of use). Low priority will in general be based on an absence of any significant concern (safety or effectiveness) based on a review of available data. A lack of data in critical areas (e.g., toxicity) will ordinarily preclude classification as

low priority.

(1) Human food safety -- High priority are:

(a) Known or suspected carcinogens;

(b) Other products known to pose a serious toxicological hazard, and

(c) Other products suspected of posing a serious toxicological hazard and that are believed to have substantial use in aquaculture.

(2) Target animal safety -- High priority for products known to pose significant concerns.

(3) Effectiveness -- High priority for products intended for therapeutic use that are known to be ineffective.

(4) Environmental and occupational effects -- High priority when there is affirmative evidence that use of the product will have a significant environmental or occupational impact and the use is not regulated adequately under other laws.

e. Intended use -- Conditions of use such as species, life stage, dosage, route of administration, etc.

f. Misuse potential -- High priority for products with a known potential for misuse, either directly in humans (e.g., anabolic steroids) or in food species.

g. Life stages -- A food species will as a general rule be considered food at all life stages. However, the life stage will be a factor in determining enforcement priority with respect to use of a drug in a particular life stage. (See 1240.4260.)

h. Regulatory considerations

(1) availability of expert support for a court case.

(2) availability of agency resources to support a regulatory action.

(3) availability of the required evidence.

5. Extent of data review for low priority determinations.

a. Safety (target animal and human food) and effectiveness

In general, only published peer reviewed studies or literature will be reviewed for the purpose of making regulatory priority determinations. Unpublished data should ordinarily be submitted in support of an NADA approval. However, unpublished data may be reviewed for enforcement priority determinations provided that, considering all the relevant circumstances, it is unlikely that the data will be submitted in support of an NADA. "Circumstances" include, for example, the conditions under which the study was conducted, the potential market for the drug, etc.

b. Environmental and occupational/user safety

Compliance with applicable Federal, State, and local laws will be made a condition of low regulatory priority status, and data will not be reviewed except where there is reason to believe that such laws do not provide adequate protection.

Either published or unpublished data may be reviewed. Information as to standard industry practices might also be reviewed, as applicable. Except in unusual circumstances, NADAs will not be required where the only concerns are environmental and occupational.

6. Individual Drug Determinations

   a. Examples of drugs with high priority for regulatory action are:

      Chloramphenicol
      Nitrofurans
      Quinolones
      Malachite Green
      Steroid Hormones

   b. Special Category (found not to be low regulatory priority but regulatory action deferred pending further study):

      Copper sulfate
      Potassium permanganate

   c. Drugs determined to be low regulatory priority (Attachment):

ATTACHMENT

LOW REGULATORY PRIORITY AQUACULTURE DRUGS

The following compounds have undergone review by the Food and Drug Administration and have been determined to be new animal drugs of low regulatory priority.

ACETIC ACID - 1000 to 2000 ppm dip for 1 to 10 minutes as a parasiticide for fish.

CALCIUM CHLORIDE - Used to increase water calcium concentration to ensure proper egg hardening. Dosages used would be those necessary to raise calcium concentration to 10-20 ppm CaC03.

- Used up to 150 ppm indefinitely to increase the hardness of water for holding and transporting fish in order to enable fish to maintain osmotic balance.

CALCIUM OXIDE - Used as an external protozoacide for fingerlings to adult fish at a concentration of 2000 mg/L for 5 seconds.

CARBON DIOXIDE GAS - For anesthetic purposes in cold, cool, and warm water fish.

FULLER'S EARTH - Used to reduce the adhesiveness of fish eggs to improve hatchability.

GARLIC (Whole Form) - Used for control of helminth and sea lice infestations of marine salmonids at all life stages.

HYDROGEN PEROXIDE - Used at 250-500 mg/L to control fungi on all species and life stages of fish, including eggs.

ICE - Used to reduce metabolic rate of fish during transport.

MAGNESIUM SULFATE - Used to treat external monogenic trematode infestations and external crustacean infestations in fish at all life stages. Used in all freshwater species. Fish are immersed in a 30,000 mg $MgS0_4$/L and 7000 mg NaCl/L solutions for 5 to 10 minutes.

ONION (Whole Form) - Used to treat external crustacean parasites, and to deter sea lice from infesting external surface of salmonids at all life stages.

PAPAIN - Use of a 0.2% solution in removing the gelatinous matrix of fish egg masses in order to improve hatchability and decrease the incidence of disease.

POTASSIUM CHLORIDE - Used as an aid in osmoregulation; relieves stress and prevents shock. Dosages used would be those necessary to increase chloride ion concentration to 10-2000 mg/L.

POVIDONE IODINE - 100 ppm solution for 10 minutes as an egg surface disinfectant during and after water hardening.

SODIUM BICARBONATE - 142-642 ppm for 5 minutes as a means of introducing carbon dioxide into the water to anesthetize fish.

SODIUM CHLORIDE - 0.5% to 1.0% solution for an indefinite period as an osmoregulatory aid for the relief of stress and prevention of shock; and 3% solution for 10 to 30 minutes as a parasiticide.

SODIUM SULFITE - 15% solution for 5 to 8 minutes to treat eggs in order to improve their hatchability.

THIAMINE HYDROCHLORIDE - Used to prevent or treat thiamine deficiency in salmonids. Eggs are immersed in an aqueous solution of up to 100 ppm for up to four hours during water hardening. Sac fry are immersed in an aqueous solution of up to 1,000 ppm for up to one hour.

UREA and TANNIC ACID - Used to denature the adhesive component of fish eggs at concentrations of 15g urea and 20g NaCl/5 liters of water for approximately 6 minutes, followed by a separate solution of 0.75g tannic acid/5 liters of water for an additional 6 minutes. These amounts will treat approximately 400,000 eggs.

The Agency is unlikely to object to the use of these substances if the following conditions are met:

(1) The substances are used for these indications;

(2) The substances are used at the prescribed levels;

(3) The substances are used according to good management practices;

(4) The product is of an appropriate grade for use in food animals, and

(5) There is not likely to be an adverse effect on the environment.

The Agency's enforcement position on the use of these substances should not be considered an approval nor an affirmation of their safety and effectiveness. Based on the information available at some time in the future, the Agency may take a different position on the use of any or all of these substances.

Classification of these substances as new animal drugs of low regulatory priority does not exempt facilities from complying with other Federal, State, and local environmental requirements. For example, facilities using these substances would still be required to comply with National Pollutant Discharge Elimination System (NPDES) requirements.

NOTE: The primary long range goals in enforcement prioritization will be to protect public health and encourage submission of INADs and NADAs with a view toward obtaining approvals to meet therapeutic and production needs in aquaculture.

(6) Labeling and GMPs for Low Priority Drugs.

a. Labeling for low priority use will not be required for a chemical that is commonly used for nondrug purposes even if the manufacturer or distributor promotes the chemical for the permitted low priority use.

b. However, a chemical that has significant animal or human drug uses in addition to the low priority aquaculture use will be required to be labeled for the low priority uses if the manufacturer or distributor establishes the intended low priority use for its product by promotion or other means.

c. Where labeling is required, all other provisions of the Act pertaining to drugs except the approval requirement will apply. This includes registration, drug listing and Current Good Manufacturing Practices (CGMPs), etc.

d. Low regulatory priority compounds may be marketed for aquaculture use with drug claims (the claims permitted for such compounds) but must be of an appropriate quality for use in food animals.

e. If drug claims appear on the product label, in product catalogs, or in promotional material, the following conditions must be met:

   o The product must have been manufactured according to CGMPs as defined in the Code of Federal Regulations;

- o The product manufacturer must be registered with the FDA; and
- o The product must be drug-listed with FDA.

f. Material deviations in labeling or promotion from the permitted low priority claims might cause a particular product to be removed from the low priority category.